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13. ABSTRACT *(Maximum 200 words)*

The long term goal of the research program of this laboratory is to reach an understanding of the physiological interactions between neurons and their associated glia that relate to their ability to cooperatively regulate the ionic and neurohumoral milieu of the perineural and/or periaxonal space. To this end we have been investigating the mechanisms by which axons and neurons generate the chemical signals during their excitation that signals the glia to activate their metabolic and uptake processes that inactivate neurotransmitters preventing their accumulation to toxic concentrations and the transport of potassium and of sodium to maintain appropriate amounts of each ion in the perineural space thereby preserving excitability properties of the neural elements of the nervous system. For these investigations we have used the intact nerve fiber - Schwann cell preparations of crayfish and squid to study nerve-Schwann cell interactions in intact systems and the mammalian Schwann cell culture to determine the generality of our findings to mammalian systems.

14. SUBJECT TERMS
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Statement of Problem:

In recent years it has been recognized that glia of the nervous system participate in the acute management of the ionic and neurohumoral milieu of the neural microenvironment. It is the glia that modulate changes in the ionic environment of nerve fibers and synaptic regions of the nervous system may influence excitability properties of nerve cells, release of transmitter, propagation velocity and safety factors for excitation and branch point action potential conduction. The questions addressed by this program of research are (1) what are the specific roles of the glia in neural microenvironment homeostasis (2) what mechanisms of communication exist between neurons and glia and (3) what changes in physiological properties of glia are induced by neural activity.

Our findings since the beginning of this project can be summarized as follows:

1. Glutamate and potassium released by the excited nerve fiber acts as the signal to the surrounding glia.

2. The release of glutamate and potassium appear to be coupled so that the quantity of glutamate released is in direct proportion to the potassium released thus providing an appropriate signal to the glial cell for the rapid clearance of the excess potassium that tends to appear in the perineural space during excitation.

3. The Schwann cell (glial cell) has, on its membrane, a specific non-MNDA (quisqualate/kainate) type glutamate which activates 2 separate processes.

   a. opening of a sodium ion channel that tends to depolarize the membrane potential of the Schwann cell. The function of this particular channel is unknown but we have speculated that the sodium that enters the glial cell under these circumstances insures that the sodium/potasssium transporter is primed for potassium uptake processes by the sodium pump.
   b. activation of an increase in intracellular ionic calcium via an inositol phosphate second messenger that is required for the release of acetylcholine from the Schwann cell. ACh acts on an Schwann cell autoreceptor, coupled to a c-AMP generating mechganism that is ultimately responsible for a chloride-dependent Schwann cell hyperpolarization.

4. The Schwann cell hyperpolarization, because it is due to a decrease in chloride permeability, decreases the efflux of potassium from the Schwann cell. This allows an increase in nerve potassium efflux to an amount equivalent to the decrease in glial potassium efflux without increasing perineural potassium concentration. When excessive activity tends to cause accumulation of potassium both sodium/potassium/2chloride cotransport activity and sodium/potassium antiport transport are also activited in the glial cell to insure that the perineural microenvironment concentration of potassium remains consistent with preservation of neural excitability.

5. Enzymes of the glutamate-glutamine neurotransmitter cycle have been

shown to exist in the intact nerve -glial cell preparation used in these studies as it has been identified in mammalian nervous systems. That is, glutamine synthetase, the enzyme required for conversion of glutamate to glutamine is almost exclusively compatmentalized to the glial cell while high concentrations of glutaminase are found in both glia and nerve. These findings are consistent with the concept that the glia have a primary role in removing neuroactive substances from the neural microenvironment before they accumulate to toxic levels. The presence of glutaminease in both cells is consistent with the metabolic importance of glutamate in general cell metabolism of all cells.

6. In keeping with the strong physiological coupling betweeen nerve cells and their associated glia and the large transport activity of the glia we have also determined that approximately 90% of the metabolic activity of intact nerve tissue can be accounted for by glial cells and that the level of acticity at any time is dependent on the metabolic state of the nerve cells.

7. In cultured mammalian Schwann cells we have determined that the normal resting membrane potential of these cells is low (about -45 mV) and similar to the resting potential of intact glia of the invertebrate nervous systems we have been using for in vivo studies.

8. In mammalian Schwann cells there is a strong coupling between the activity of the sodium/potassium/2 chloride cotransporter and the sodium pump. Increasing c-AMP of the Schwann cell activates both transporter systems. A long term requirement for high sodium pump activity results in an increase in its activity through the process of translocation of sequestered intracellular pump molecules to the plasma membrane.

9. Most recently we have been examining the manner in which mammalian glia deal with proton transport and have found them to be active pH buffers for extracellular space in addition to the requirement to maintain intracellular pH for intracellular enzymatic activity.

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No inventions resulted from the research supported under this grant nor subcontracts entered into.